INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

# Molecular Docking Studies in Type 2 Diabetes Mellitus Drug Discovery: A Chemist's Perspective on Computational Design and Visual Analytics

**Dr. Bolie Therattil***

*Associate Professor in Chemistry, St Aloysius College (affiliated to University of Calicut), Elthuruth, Thrissur, India*

ARTICLE INFO

Published: 31 July 2026
Keywords:
Molecular docking, Type 2 diabetes mellitus, Drug discovery, Computational chemistry, Visual computing, Structure-based drug design, ADMET, Machine learning.
DOI:
10.5281/zenodo.21726913

## ABSTRACT

Type 2 diabetes mellitus (T2DM) represents a global health crisis requiring innovative therapeutic strategies. Molecular docking has emerged as a cornerstone computational technique in modern drug discovery, enabling rapid virtual screening, rational ligand design, and mechanistic understanding of protein-ligand interactions at atomic resolution. This comprehensive review examines molecular docking methodologies applied to T2DM drug discovery from a medicinal chemist's perspective, emphasizing the integration of visual computing technologies. We systematically analyze docking studies targeting key enzymatic and receptor systems: including dipeptidyl peptidase-4 (DPP-4), α-glucosidase, α-amylase, protein tyrosine phosphatase 1B (PTP1B), peroxisome proliferator-activated receptor gamma (PPAR-γ), glucose transporters (GLUT), sodium-glucose cotransporter 2 (SGLT2), and aldose reductase. The review critically evaluates docking algorithms, scoring functions, force fields, and virtual screening pipelines while highlighting chemist-centric considerations: including pharmacophore modeling, structure-activity relationships (SAR), ADMET profiling, and lead optimization strategies. We explore the transformative role of visual computing in 3D molecular visualization, binding pocket analysis, and interaction fingerprinting. The review organizes representative studies by target class, revealing scaffold diversity, binding modes, and quantitative affinity data. The integration of machine learning and artificial intelligence with traditional docking workflows the review discusses as an emerging paradigm. Finally, we address current limitations including scoring function accuracy, protein flexibility representation, and solvation modeling while proposing future directions toward multi-target docking, fragment-based design, and AI-driven generative chemistry for next-generation antidiabetic therapeutics.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) has emerged as one of the most pressing global health challenges

***Corresponding Author:** Dr. Bolie Therattil
**Address:** *Associate Professor in Chemistry, St Aloysius College, Elthuruth, Thrissur, India*
**Email** : btherattil@gmail.com

**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

of the 21st century, affecting over 537 million adults worldwide as of 2021, with projections indicating a rise to 783 million by 2045. This metabolic disorder, characterized by insulin resistance and progressive β-cell dysfunction, leads to chronic hyperglycemia and severe complications including cardiovascular disease, nephropathy, retinopathy, and neuropathy. Despite the availability of multiple therapeutic classes—including biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists—the need for novel antidiabetic agents with improved efficacy, safety profiles, and reduced side effects remains critical.

The advent of computational drug discovery has revolutionized the pharmaceutical landscape, offering rapid, cost-effective alternatives to traditional high-throughput screening. Among computational methodologies, molecular docking stands as a cornerstone technique, enabling researchers to predict the binding modes and affinities of small molecules to protein targets at atomic resolution. By simulating the physical interactions between ligands and macromolecular receptors, docking facilitates virtual screening of vast chemical libraries, rational design of lead compounds, and mechanistic elucidation of drug action.

From a medicinal chemist's perspective, molecular docking transcends mere computational prediction—it serves as an integrated platform for hypothesis generation, structure-activity relationship (SAR) analysis, and iterative optimization. The synergy between docking predictions and experimental validation accelerates the drug discovery timeline, reduces attrition rates, and enhances the probability of identifying clinically viable candidates. Moreover, the integration of visual computing technologies has transformed how chemists interact with molecular data, enabling intuitive 3D visualization, dynamic binding pocket analysis, and comprehensive interaction mapping.

This review provides a comprehensive examination of molecular docking applications in T2DM drug discovery, emphasizing methodological rigor, chemical insights, and visual analytics. We systematically explore key therapeutic targets, dissect docking algorithms and scoring functions, analyze representative studies across target classes, and discuss the transformative impact of machine learning integration. By addressing current limitations and proposing future directions, this work aims to guide researchers toward more effective computational strategies for next-generation antidiabetic therapeutics.

## 2. The Global Burden of Type 2 Diabetes Mellitus and the Imperative for Computational Drug Design

Type 2 diabetes mellitus (T2DM) represents a multifactorial metabolic disorder arising from complex interactions between genetic predisposition, environmental factors, and lifestyle choices. The pathophysiology involves peripheral insulin resistance, impaired insulin secretion from pancreatic β-cells, and dysregulated hepatic glucose production. Chronic hyperglycaemia triggers oxidative stress, advanced glycation end-product (AGE) formation, and inflammatory cascades, culminating in microvascular and macrovascular complications that significantly reduce quality of life and life expectancy.

Current pharmacological interventions target diverse mechanisms: metformin enhances insulin sensitivity and suppresses hepatic gluconeogenesis; sulfonylureas stimulate insulin

secretion; thiazolidinediones activate PPAR-γ to improve insulin sensitivity; DPP-4 inhibitors prolong incretin hormone activity; SGLT2 inhibitors promote renal glucose excretion; and GLP-1 receptor agonists enhance glucose-dependent insulin secretion. However, these therapies are associated with limitations, including gastrointestinal disturbances, hypoglycaemia risk, weight gain, cardiovascular concerns, and variable patient responses.

The imperative for novel therapeutic agents has driven the pharmaceutical industry towards structure-based drug design (SBDD) and ligand-based drug design (LBDD) approaches. Molecular docking, as a central SBDD technique, leverages three-dimensional structural information of target proteins—obtained through X-ray crystallography, NMR spectroscopy, or cryo-electron microscopy—to computationally predict ligand binding. This approach offers several advantages: (1) rapid screening of millions of compounds within days, (2) identification of novel chemical scaffolds beyond known pharmacophores, (3) mechanistic insights into binding interactions guiding rational optimization, and (4) cost reduction by prioritizing compounds for experimental validation.

Recent advances in computational power, algorithm development, and structural biology have positioned molecular docking as an indispensable tool in modern drug discovery. The availability of high-resolution crystal structures for key T2DM targets—including DPP-4, α-glucosidase, PTP1B, and PPAR-γ—has enabled structure-guided campaigns that have yielded clinical candidates and approved drugs. Furthermore, the integration of docking with complementary techniques such as molecular dynamics (MD) simulations, free energy calculations, and ADMET prediction creates comprehensive workflows that bridge computational predictions with experimental outcomes.

## 3. Key Enzymatic and Protein Targets in T2DM Therapy

### 3.1 α-Glucosidase and α-Amylase

α-Glucosidase and α-amylase represent critical enzymes in carbohydrate metabolism, catalyzing the hydrolysis of complex polysaccharides and oligosaccharides into absorbable monosaccharides. α-Amylase initiates starch digestion in the oral cavity and small intestine, while α-glucosidase, located in the brush border of the small intestine, performs the final step of carbohydrate digestion by cleaving α-1,4-glycosidic bonds in disaccharides and oligosaccharides. Inhibition of these enzymes delays glucose absorption, attenuates postprandial hyperglycemia, and reduces glycemic excursions—a therapeutic strategy validated by approved drugs such as acarbose, miglitol, and voglibose.

Molecular docking studies targeting α-glucosidase have identified diverse chemical scaffolds with inhibitory potential. Ndarawit et al. conducted a comprehensive virtual screening of the Natural Products Activity and Species (NPASS) database comprising 30,926 compounds, identifying NPC204580 (Chrotacumine C) and NPC137813 (1-O-(2-Methoxy-4-Acetylphenyl)-6-O-(E-Cinnamoyl)-Beta-D-Glucopyranoside) as dual α-amylase/α-glucosidase inhibitors with binding energies of -14.46 kcal/mol and -12.58 kcal/mol for α-amylase, and -8.42 kcal/mol and -8.76 kcal/mol for α-glucosidase, respectively (Ndarawit et al., 2024). These compounds exhibited ionic interactions, hydrogen bonding, and hydrophobic contacts with critical active site residues, with 100 ns molecular

dynamics simulations confirming complex stability through RMSD, RMSF, and MM-GBSA analyses (Ndarawit et al., 2024).

Triazole derivatives have emerged as privileged scaffolds for α-glucosidase inhibition. Abchir et al. employed an integrative approach combining 3D-QSAR, molecular docking, ADMET analysis, and molecular dynamics to design novel triazole-based inhibitors (Abchır et al., 2024). Their multiple linear regression (MLR) model ($Q^2 = 0.652$, $R^2 = 0.954$) identified key structural determinants of inhibitory activity, leading to the design of three compounds with high biological activity, strong binding affinity, and favorable oral bioavailability (Abchır et al., 2024). The study utilized MM-GBSA calculations to assess binding free energies, revealing favorable thermodynamic profiles (Abchır et al., 2024).

Flavonoids represent another extensively studied class. Proença et al. investigated flavonoid inhibition of α-glucosidase through combined in vitro and in silico approaches, establishing structure-activity relationships that correlated hydroxylation patterns and glycosylation with inhibitory potency (Proença et al., 2017). Computational studies by Shah et al. explored plant-derived terpenes as α-glucosidase inhibitors, leveraging molecular docking to identify lead compounds from natural product libraries (Shah et al., 2021).

The integration of QSAR modeling with docking has enhanced predictive accuracy. Naanaai et al. designed novel antidiabetic agents using 3D-QSAR (CoMSIA), molecular docking, ADMET analysis, molecular dynamics, and ligand transport simulations, focusing on Indenoquinoxaline-phenylacrylohydrazide hybrids (Naanaai et al., 2025). Their workflow demonstrated the value of multi-technique integration in identifying compounds with optimal binding profiles and pharmacokinetic properties (Naanaai et al., 2025).

Dual inhibition of α-glucosidase and α-amylase offers synergistic therapeutic benefits by targeting multiple steps in carbohydrate digestion. Sulong et al. investigated metformin derivatives as α-glucosidase inhibitors through computational analysis and molecular dynamics simulations, exploring structural modifications to enhance potency (Sulong et al., 2025). Tong et al. employed QSAR, molecular docking, and molecular dynamics to design novel α-glucosidase inhibitors, identifying compounds with superior binding affinities compared to acarbose (Tong et al., 2024).

### 3.2 Dipeptidyl Peptidase-4 (DPP-4)

Dipeptidyl peptidase-4 (DPP-4) is a serine protease that degrades incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which stimulate insulin secretion in a glucose-dependent manner. DPP-4 inhibitors (gliptins) prolong incretin activity, enhance insulin secretion, suppress glucagon release, and improve glycemic control without significant hypoglycemia risk. Approved DPP-4 inhibitors include sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.

The crystal structure of DPP-4 (PDB: 1X70, 2ONC, among others) reveals a catalytic triad (Ser630, Asp708, His740) and a large hydrophobic S1 pocket that accommodates substrate side chains. Molecular docking studies have exploited these structural features to design novel inhibitors. Chen et al. performed structure-based molecular docking and molecular dynamics simulations to identify DPP-4 inhibitors for T2DM, analyzing binding modes and stability of protein-ligand complexes (Chen et al., 2023). Their study

emphasized the importance of interactions with the catalytic triad and S1 pocket residues (Chen et al., 2023).

Akinwumi et al. conducted in silico discovery of DPP-4 inhibitors from African medicinal plants using molecular docking, ADMET analysis, molecular dynamics simulations, and MM-GBSA calculations (Akinwumi et al., 2025). The study identified natural product candidates with favorable binding energies and pharmacokinetic profiles, demonstrating the potential of ethnopharmacological resources in drug discovery (Akinwumi et al., 2025).

Computational design of trelagliptin analogues has been explored through QSAR and molecular docking approaches, aiming to optimize binding affinity and selectivity [10]. The integration of pharmacophore modeling with docking enables identification of essential chemical features for DPP-4 inhibition, guiding scaffold hopping and bioisosteric replacement strategies.

Multi-target studies have investigated compounds with dual DPP-4 and aldose reductase inhibitory activities. Balogun et al. employed cheminformatics to identify modulators of key carbohydrate-metabolizing enzymes from Crescentia cujete, revealing compounds with activity against DPP-4, α-glucosidase, and PTP1B (Balogun et al., 2023). Such polypharmacological approaches address multiple pathogenic mechanisms simultaneously, potentially offering superior therapeutic outcomes.

### 3.3 Protein Tyrosine Phosphatase 1B (PTP1B)

Protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of insulin signaling, dephosphorylating the insulin receptor and insulin receptor substrate proteins, thereby attenuating insulin sensitivity. Genetic knockout studies in mice have demonstrated that PTP1B deficiency enhances insulin sensitivity and protects against diet-induced obesity, validating PTP1B as a therapeutic target for T2DM and metabolic syndrome.

The catalytic domain of PTP1B contains a deep active site pocket with a phosphotyrosine-binding loop (P-loop) featuring the signature motif $(H/V)C(X)_5R(S/T)$. Molecular docking studies have focused on designing inhibitors that occupy this pocket while achieving selectivity over other phosphatases. Verma et al. conducted molecular docking-assisted 3D-QSAR studies of benzylidene-2,4-thiazolidinedione derivatives as PTP1B inhibitors, establishing quantitative relationships between structural features and inhibitory potency (Verma & Thareja, 2016). Their study identified key pharmacophoric elements including the thiazolidinedione core and benzylidene substituents (Verma & Thareja, 2016).

Ogunyemi et al. integrated machine learning-based QSAR with molecular modeling to identify promising PTP1B modulators from Ocimum gratissimum for T2DM therapy (Ogunyemi et al., 2025). The study employed multiple machine learning algorithms to predict inhibitory activity, followed by molecular docking and dynamics simulations to validate binding modes (Ogunyemi et al., 2025). This hybrid approach exemplifies the synergy between data-driven and physics-based methods.

Natural products have been extensively explored as PTP1B inhibitor scaffolds. Balogun et al. identified chlorogenic acid as a potent PTP1B inhibitor with binding affinity of -48.740 kcal/mol, superior to reference compounds (Balogun et al., 2023). The study employed molecular docking with AutoDock Vina, followed by 100 ns molecular dynamics simulations using AMBER

18 with FF18SB force field (Balogun et al., 2023). Post-dynamics analysis revealed stable binding with favorable MM/GBSA free energies (Balogun et al., 2023).

The challenge in PTP1B inhibitor design lies in achieving cell permeability while maintaining potency, as the active site is highly polar. Computational approaches integrating docking with ADMET prediction help identify compounds with balanced properties suitable for oral bioavailability.

### 3.4 Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ)

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a nuclear receptor that regulates genes involved in glucose metabolism, lipid homeostasis, and adipocyte differentiation. PPAR-γ agonists, such as thiazolidinediones (pioglitazone, rosiglitazone), enhance insulin sensitivity by promoting adipogenesis, increasing glucose uptake, and modulating inflammatory pathways. However, adverse effects including weight gain, fluid retention, and cardiovascular concerns have limited their use.

Molecular docking studies targeting PPAR-γ aim to identify selective modulators with improved safety profiles. Patil et al. performed computational assessment of substituted 2-mercaptobenzimidazole Schiff base derivatives targeting α-amylase, α-glucosidase, and PPAR-γ receptor in T2DM (Patil et al., 2025). The study employed molecular docking to evaluate binding modes within the PPAR-γ ligand-binding domain, identifying compounds with favorable interactions with key residues in the activation function-2 (AF-2) helix (Patil et al., 2025).

The PPAR-γ ligand-binding pocket is large and Y-shaped, accommodating diverse chemical scaffolds. Docking studies have explored partial agonists and selective modulators that activate PPAR-γ without inducing full agonist-associated side effects. Structure-based design leveraging crystal structures of PPAR-γ in complex with various ligands (PDB: 2PRG, 3DZY, among others) has guided the development of compounds with tailored efficacy and safety profiles.

### 3.5 Glucose Transporters (GLUT) and SGLT2

Glucose transporters facilitate cellular glucose uptake through facilitated diffusion (GLUT family) or active transport (SGLT family). GLUT4, the insulin-responsive glucose transporter, mediates glucose uptake in muscle and adipose tissue. Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal tubule of the kidney, reabsorbs filtered glucose. SGLT2 inhibitors (gliflozins) promote urinary glucose excretion, lowering blood glucose independently of insulin.

While SGLT2 inhibitors have achieved clinical success (canagliflozin, dapagliflozin, empagliflozin), molecular docking studies targeting SGLT2 remain limited due to the lack of high-resolution crystal structures. Homology modeling based on bacterial homologs has enabled structure-based design efforts. Computational studies have explored binding modes of gliflozins within the glucose-binding site, identifying key interactions with residues involved in substrate recognition and sodium coordination.

GLUT4 represents another potential target, with research focusing on compounds that enhance GLUT4 translocation to the plasma membrane or increase its expression. Molecular docking studies have investigated natural products and synthetic compounds that modulate GLUT4 activity, although structural challenges persist due to the transmembrane nature of the protein.

### 3.6 Aldose Reductase and Other Targets

Aldose reductase (AR) catalyzes the reduction of glucose to sorbitol in the polyol pathway, a process implicated in diabetic complications including retinopathy, neuropathy, and nephropathy. AR inhibitors aim to prevent sorbitol accumulation and osmotic stress in tissues. Muppalaneni et al. conducted virtual screening of plant-derived compounds for aldose reductase inhibition using molecular docking with multiple software platforms (GOLD, AutoDock Vina, eHiTS, PatchDock, MEDock) (Muppalaneni & Rao, 2012). Consensus scoring identified allium38 as a lead compound with high binding affinity (MolDock Score: -146.111 kcal/mol) and eight hydrogen bond interactions with key residues including Thr113, His110, Val47, and Gln49 (Muppalaneni & Rao, 2012).

Balogun et al. identified luteolin as a potent aldose reductase inhibitor with binding affinity of -9.9 kcal/mol, demonstrating structural stability and compactness through molecular dynamics simulations (Balogun et al., 2023). The study proposed luteolin as a multi-target candidate against T2DM and diabetic retinopathy (Balogun et al., 2023).

Additional targets explored in molecular docking studies include glycogen phosphorylase, which regulates glycogen breakdown; glucokinase, a key enzyme in glucose sensing; and various inflammatory mediators implicated in insulin resistance. The diversity of targets reflects the multifactorial nature of T2DM and the potential for polypharmacological interventions.

## 4. Molecular Docking Methodology: Foundations and Implementations

### 4.1 Docking Algorithms and Search Strategies

Molecular docking algorithms address the fundamental challenge of predicting the optimal binding pose of a ligand within a protein binding site—a problem involving exploration of a vast conformational space defined by translational, rotational, and torsional degrees of freedom. The computational complexity scales exponentially with the number of rotatable bonds, necessitating efficient search strategies that balance exploration and exploitation.

**Systematic Search Methods** exhaustively sample conformational space by incrementally varying ligand degrees of freedom. DOCK, one of the earliest docking programs, employs incremental construction, building the ligand within the binding site by sequentially adding fragments and optimizing their positions. While systematic approaches guarantee identification of the global minimum within the sampled space, their computational cost becomes prohibitive for flexible ligands with numerous rotatable bonds.

**Stochastic Search Methods** employ randomized algorithms to explore conformational space efficiently. Genetic algorithms (GAs), implemented in GOLD (Genetic Optimization for Ligand Docking), encode ligand conformations as chromosomes and evolve populations through selection, crossover, and mutation operations. AutoDock utilizes a Lamarckian genetic algorithm combining GA with local search, enabling efficient exploration of rugged energy landscapes. Simulated annealing, employed in ICM and other programs, applies a temperature-based acceptance criterion to escape local minima.

**Gradient-Based Optimization** methods, such as those in Glide (Schrödinger), employ energy minimization algorithms to refine ligand poses. These approaches are computationally efficient but risk convergence to local minima, necessitating multiple starting configurations.

**Incremental Construction** algorithms, exemplified by FlexX and DOCK, fragment the ligand into rigid components and flexible linkers, placing base fragments in the binding site and incrementally adding remaining fragments while optimizing torsional angles. This approach reduces conformational complexity but requires careful selection of fragmentation points.

**Monte Carlo Methods** randomly sample conformational space, accepting or rejecting moves based on energy criteria. AutoDock Vina employs a sophisticated Monte Carlo algorithm with local optimization, achieving superior speed and accuracy compared to earlier AutoDock versions.

Recent studies in T2DM drug discovery have employed diverse docking algorithms. Ndarawit et al. utilized molecular docking to screen the NPASS database, though specific software details were not disclosed (Ndarawit et al., 2024). Muppalaneni et al. compared multiple docking programs (GOLD, AutoDock Vina, eHiTS, PatchDock, MEDock) using consensus scoring to enhance prediction reliability (Muppalaneni & Rao, 2012). Balogun et al. employed AutoDock Vina for initial docking, followed by 100 ns molecular dynamics simulations with AMBER 18 (Balogun et al., 2023).

### 4.2 Scoring Functions: Empirical, Knowledge-Based, and Physics-Based Approaches

Scoring functions evaluate the binding affinity of protein-ligand complexes, serving dual roles: (1) guiding conformational search during docking, and (2) ranking compounds in virtual screening. The accuracy of scoring functions critically determines docking success, yet remains a significant challenge due to the complexity of molecular recognition.

**Force Field-Based Scoring Functions** compute binding energy using molecular mechanics force fields, summing van der Waals, electrostatic, hydrogen bonding, and desolvation terms. AutoDock employs a semi-empirical force field calibrated against experimental binding data, incorporating terms for dispersion/repulsion, hydrogen bonding, electrostatics, and desolvation. AMBER and CHARMM force fields, widely used in molecular dynamics, have been adapted for docking applications. While physically rigorous, force field-based scoring is computationally intensive and sensitive to parameterization.

**Empirical Scoring Functions** fit binding affinity to weighted sums of interaction terms derived from regression analysis of experimental data. ChemScore, implemented in GOLD, decomposes binding free energy into contributions from hydrogen bonds, metal-ligand interactions, lipophilic contacts, and ligand flexibility penalties. GlideScore (Schrödinger) employs a similar empirical framework with terms for hydrophobic enclosure, π-π stacking, and rotatable bond penalties. Empirical functions offer computational efficiency and reasonable accuracy but may suffer from limited transferability beyond training sets.

**Knowledge-Based Scoring Functions** derive interaction potentials from statistical analysis of protein-ligand complex structures in databases such as the Protein Data Bank (PDB). PMF (Potential of Mean Force) scoring, implemented in DOCK and other programs, calculates atom-pair interaction energies based on observed distance distributions. DrugScore and SMoG employ similar statistical potentials. Knowledge-based functions capture implicit solvation and entropic effects but depend on database quality and coverage.

**Consensus Scoring** combines predictions from multiple scoring functions to improve accuracy

and reduce false positives. Muppalaneni et al. employed consensus scoring across GOLD, AutoDock Vina, eHiTS, PatchDock, and MEDock, using rank-sum techniques to identify robust hits (Muppalaneni & Rao, 2012). This approach mitigates individual scoring function biases and enhances virtual screening reliability.

**Machine Learning Enhanced Scoring** represents an emerging paradigm. Ogunyemi et al. integrated machine learning-based QSAR with molecular docking to predict PTP1B inhibitory activity (Ogunyemi et al., 2025). Deep learning models trained on large datasets of protein-ligand complexes have demonstrated superior binding affinity prediction compared to classical scoring functions, though interpretability and generalization remain challenges.

### 4.3 Force Fields and Energy Minimization

Force fields define the potential energy surface governing molecular interactions, comprising bonded terms (bond stretching, angle bending, torsional rotation) and non-bonded terms (van der Waals, electrostatics). Accurate force field parameterization is essential for reliable docking predictions and subsequent molecular dynamics simulations.

**AMBER (Assisted Model Building with Energy Refinement)** force fields, including ff14SB, ff18SB, and GAFF (General AMBER Force Field), are widely employed in biomolecular simulations. Balogun et al. utilized AMBER 18 with FF18SB variant and GAFF for 100 ns molecular dynamics simulations of T2DM enzyme inhibitors (Balogun et al., 2023). RESP (Restrained Electrostatic Potential) charges were computed to accurately represent electrostatic interactions (Balogun et al., 2023).

**CHARMM (Chemistry at HARvard Macromolecular Mechanics)** force fields, particularly CHARMM36, offer comprehensive parameterization for proteins, nucleic acids, lipids, and small molecules. CHARMM-based docking and dynamics simulations provide consistent energetics across different molecular systems.

**OPLS (Optimized Potentials for Liquid Simulations)** force fields, developed by Jorgensen and colleagues, are optimized for reproducing condensed-phase properties. OPLS-AA (all-atom) and OPLS3e (enhanced version) are implemented in Schrödinger's Maestro suite, supporting Glide docking and Desmond molecular dynamics.

**GROMOS (GROningen MOlecular Simulation)** force fields are optimized for biomolecular simulations in aqueous solution, with united-atom representations reducing computational cost.

Energy minimization algorithms refine docked poses by relaxing steric clashes and optimizing geometry. Steepest descent, conjugate gradient, and limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) algorithms are commonly employed. Minimization typically proceeds in stages: initial minimization with restrained protein atoms, followed by full system relaxation.

### 4.4 Virtual Screening Pipelines and Workflow Design

Virtual screening (VS) workflows integrate multiple computational techniques to identify hit compounds from large chemical libraries. Effective pipeline design balances computational efficiency, prediction accuracy, and chemical diversity.

**Ligand Preparation** involves generating 3D coordinates, assigning protonation states at

physiological pH, enumerating tautomers and stereoisomers, and energy minimization. LigPrep (Schrödinger), OpenBabel, and RDKit are commonly used tools. Ndarawit et al. screened the NPASS database (30,926 compounds) after filtering for drug-likeness and toxicity (Ndarawit et al., 2024).

**Protein Preparation** includes adding hydrogen atoms, assigning protonation states to ionizable residues, optimizing hydrogen bond networks, removing crystallographic waters (or retaining conserved waters), and energy minimization. Protein Preparation Wizard (Schrödinger), UCSF Chimera, and MOE (Molecular Operating Environment) facilitate these steps.

**Binding Site Definition** specifies the docking region, typically centered on co-crystallized ligands or identified through cavity detection algorithms (SiteMap, fpocket, DoGSiteScorer). Grid-based methods pre-calculate interaction energies on a 3D grid, accelerating docking calculations.

**Hierarchical Filtering** employs sequential filters of increasing computational cost: (1) pharmacophore screening to identify compounds with essential features, (2) rapid docking with simplified scoring, (3) refined docking with accurate scoring, (4) post-docking optimization and rescoring, and (5) molecular dynamics simulations for top hits. This funnel approach efficiently narrows millions of compounds to dozens of candidates for experimental testing.

**Post-Docking Analysis** includes visual inspection of binding modes, interaction analysis (hydrogen bonds, hydrophobic contacts, π-π stacking), binding free energy calculations (MM-GBSA, MM-PBSA), and clustering to identify diverse scaffolds. Abchir et al. employed MM-GBSA calculations to assess binding free energies of triazole derivatives (Abchır et al., 2024).

**Molecular Dynamics Validation** subjects docked complexes to MD simulations, assessing stability through RMSD, RMSF, radius of gyration, and hydrogen bond occupancy. Ndarawit et al. performed 100 ns MD simulations, confirming stability of lead compounds through RMSD, RMSF, and GBSA energy analyses (Ndarawit et al., 2024). Balogun et al. employed AMBER 18 for 100 ns simulations with isobaric-isothermal ensemble, using PTRAJ and CPPTRAJ for trajectory analysis (Balogun et al., 2023).

Representative workflows in T2DM research demonstrate integration of multiple techniques. Naanaai et al. combined 3D-QSAR (CoMSIA), molecular docking, ADMET analysis, molecular dynamics, ligand transport (CaverDock), and retrosynthesis to design α-glucosidase inhibitors (Naanaai et al., 2025). This comprehensive approach exemplifies modern computational drug discovery paradigms.

## 5. The Chemist's Perspective on Ligand Design

### 5.1 Pharmacophore Modeling and Feature Identification

Pharmacophore modeling identifies the spatial arrangement of chemical features essential for biological activity, serving as a template for virtual screening and de novo design. A pharmacophore comprises hydrogen bond donors/acceptors, hydrophobic regions, aromatic rings, positive/negative ionizable groups, and metal coordination sites.

**Structure-Based Pharmacophores** derive features from protein-ligand complex structures, mapping interaction points between ligand atoms and protein residues. LigandScout, Phase

(Schrödinger), and Discovery Studio generate structure-based pharmacophores automatically from crystal structures or docked poses.

**Ligand-Based Pharmacophores** align active compounds to identify common features, applicable when protein structures are unavailable. Alignment algorithms (flexible vs. rigid) and feature weighting schemes influence model quality.

In T2DM research, pharmacophore modeling has guided inhibitor design across multiple targets. For α-glucosidase, essential features include hydrogen bond donors interacting with catalytic residues (Asp215, Glu277, Asp352 in human α-glucosidase) and hydrophobic regions occupying substrate-binding subsites. Proença et al. established structure-activity relationships for flavonoid α-glucosidase inhibitors, identifying hydroxylation patterns critical for activity (Proença et al., 2017).

For DPP-4, pharmacophores emphasize interactions with the catalytic triad (Ser630, Asp708, His740) and hydrophobic contacts within the S1 pocket. Aromatic or hydrophobic groups occupying the S1 pocket enhance potency and selectivity. Chen et al. analyzed DPP-4 inhibitor binding modes, highlighting key interaction points (Chen et al., 2023).

PTP1B pharmacophores focus on the phosphotyrosine-binding pocket, requiring negatively charged or polar groups to mimic phosphate interactions, along with hydrophobic extensions into adjacent pockets. Verma et al. identified pharmacophoric elements in benzylidene-2,4-thiazolidinedione derivatives, including the thiazolidinedione core and benzylidene substituents (Verma & Thareja, 2016).

### 5.2 Structure-Activity Relationships (SAR) and Scaffold Optimization

Structure-activity relationships (SAR) correlate chemical structure with biological activity, guiding iterative optimization of lead compounds. Quantitative SAR (QSAR) employs statistical models to predict activity from molecular descriptors, while qualitative SAR identifies trends from experimental data.

**3D-QSAR** methods, including CoMFA (Comparative Molecular Field Analysis) and CoMSIA (Comparative Molecular Similarity Indices Analysis), correlate 3D molecular fields with activity. Naanaai et al. generated a CoMSIA model ($Q^2$ = 0.652, $R^2$ = 0.954) for Indenoquinoxaline-phenylacrylohydrazide hybrids as α-glucosidase inhibitors, identifying structural determinants of potency (Naanaai et al., 2025). Abchir et al. employed multiple linear regression (MLR) for QSAR analysis of triazole derivatives, achieving $Q^2$ = 0.652 and $R^2$ = 0.954 (Abchır et al., 2024).

**Scaffold Hopping** replaces core structures while maintaining pharmacophoric features, accessing novel chemical space and improving intellectual property positions. Bioisosteric replacement substitutes functional groups with similar physicochemical properties (e.g., carboxylic acid → tetrazole, benzene → pyridine), modulating potency, selectivity, and ADMET properties.

**Fragment-Based Design** identifies small molecular fragments binding weakly to target sites, then links or grows fragments into potent leads. This approach explores chemical space efficiently and often yields ligand-efficient compounds.

SAR studies in T2DM research have revealed key trends. For α-glucosidase inhibitors, electron-

withdrawing substituents on aromatic rings enhance activity, while bulky hydrophobic groups improve binding affinity. Firdaus et al. reviewed pyrazole scaffold-based α-glucosidase inhibitors, summarizing SAR and synthetic routes [16]. For DPP-4 inhibitors, β-amino acid derivatives with hydrophobic side chains show enhanced potency, while fluorinated substituents improve metabolic stability.

### 5.3 ADMET Profiling and Drug-Likeness Assessment

ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) profiling predicts pharmacokinetic and safety properties, enabling early identification of compounds with drug-like characteristics. Computational ADMET tools accelerate lead optimization by filtering compounds with poor bioavailability or toxicity liabilities.

**Absorption** predictions assess oral bioavailability through parameters including intestinal permeability (Caco-2, MDCK models), P-glycoprotein efflux, and solubility. Lipinski's Rule of Five (molecular weight ≤ 500 Da, logP ≤ 5, hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10) provides a simple filter for oral drug-likeness. Balogun et al. reported that 12 of 14 compounds passed Lipinski's rule, with bioavailability scores above 20% for 11 compounds (Balogun et al., 2023).

**Distribution** models predict plasma protein binding, blood-brain barrier (BBB) penetration, and volume of distribution. For T2DM drugs, BBB penetration is generally undesirable to minimize central nervous system side effects.

**Metabolism** predictions identify sites of cytochrome P450-mediated oxidation, conjugation reactions, and metabolic stability. CYP450 isoform inhibition/induction predictions assess drug-drug interaction risks.

**Excretion** models estimate renal clearance and half-life, informing dosing regimens.

**Toxicity** predictions screen for hepatotoxicity, cardiotoxicity (hERG channel inhibition), mutagenicity (Ames test), and other adverse effects.

**Computational Tools** for ADMET prediction include SwissADME, pkCSM, admetSAR, and QikProp (Schrödinger). Balogun et al. employed the SWISS ADME server to predict pharmacokinetic profiles, reporting that benzoic acid achieved the highest bioavailability score (85%), while chlorogenic acid and several glycosides showed low gastrointestinal absorption (Balogun et al., 2023). Ndarawit et al. screened compounds for drug-likeness and toxicity profiles, identifying two molecules with encouraging pharmacokinetics (Ndarawit et al., 2024).

**Veber's Rules** (rotatable bonds ≤ 10, polar surface area ≤ 140 Ų) complement Lipinski's criteria, emphasizing molecular flexibility and polarity. Egan's Rule and Ghose Filter provide alternative drug-likeness criteria.

Integration of ADMET profiling with docking workflows enables holistic assessment of compound quality. Naanaai et al. incorporated ADMET analysis into their multi-technique pipeline for designing α-glucosidase inhibitors (Naanaai et al., 2025). Abchir et al. assessed pharmacokinetic properties of designed triazole derivatives, identifying three compounds suitable for oral administration (Abchır et al., 2024).

### 5.4 Lead Optimization Strategies

Lead optimization transforms initial hits into clinical candidates through iterative cycles of

design, synthesis, and testing. Computational methods guide optimization by predicting the effects of structural modifications on potency, selectivity, and ADMET properties.

**Potency Enhancement** employs strategies including: (1) optimizing interactions with key residues through hydrogen bond donors/acceptors, (2) filling hydrophobic pockets with lipophilic substituents, (3) introducing conformational constraints to reduce entropic penalties, and (4) exploiting water-mediated interactions or displacing unfavorable waters.

**Selectivity Optimization** targets differences between related proteins (e.g., PTP1B vs. other phosphatases) by exploiting unique residues in binding sites. Structural alignment and sequence analysis identify selectivity determinants.

**ADMET Optimization** addresses liabilities through: (1) modulating lipophilicity (logP) to balance permeability and solubility, (2) reducing molecular weight and rotatable bonds to improve oral bioavailability, (3) introducing metabolic blocking groups to enhance stability, (4) replacing toxic substructures (e.g., anilines, hydrazines) with safer alternatives, and (5) optimizing pKa to ensure appropriate ionization at physiological pH.

**Multi-Parameter Optimization (MPO)** balances competing objectives (potency, selectivity, ADMET, synthetic accessibility) using scoring functions that weight individual parameters. Ligand efficiency metrics (LE, LLE, LELP) guide optimization toward compounds with favorable potency-to-size ratios.

Computational tools supporting lead optimization include FEP (Free Energy Perturbation) calculations for accurate binding affinity predictions, molecular dynamics simulations for assessing binding stability, and generative AI models for proposing novel analogues. Askarzadeh et al. designed, synthesized, and evaluated phthalimide-benzenesulfonamide hybrids as α-glucosidase inhibitors, integrating in vitro testing with docking and molecular dynamics to guide optimization (Askarzadeh et al., 2022).

## 6. Visual Computing Contributions to Molecular Docking

### 6.1 3D Molecular Visualization and Interactive Analysis

Visual computing technologies have revolutionised how chemists interact with molecular docking data, transforming abstract numerical predictions into intuitive 3D representations that facilitate hypothesis generation and decision-making. Modern visualisation platforms enable real-time manipulation of protein-ligand complexes, interactive exploration of binding modes, and dynamic analysis of molecular interactions.

**Molecular Graphics Software** including PyMOL, Chimera/ChimeraX, VMD (Visual Molecular Dynamics), and Maestro (Schrödinger) provides comprehensive visualisation capabilities. These tools render proteins as cartoons, ribbons, or surfaces, while ligands are displayed as sticks, balls-and-sticks, or space-filling models. Colour coding by atom type, residue type, or property (e.g., hydrophobicity, electrostatic potential) enhances interpretability.

**Interactive Docking** allows chemists to manually position ligands within binding sites, providing intuitive understanding of steric constraints and interaction opportunities. Coot and Maestro support interactive ligand placement and real-time energy evaluation.

**Surface Representations** visualise binding pockets as molecular surfaces coloured by electrostatic potential, hydrophobicity, or shape complementarity. Connolly surfaces and solvent-accessible surfaces reveal pocket topology and druggability. SiteMap (Schrödinger) calculates binding site properties including volume, hydrophobicity, and hydrogen bonding potential.

**Stereo Visualisation** and virtual reality (VR) platforms provide immersive 3D experiences, enhancing spatial understanding of complex binding modes. VR-enabled molecular modelling tools (e.g., Nanome, ProteinVR) allow chemists to "walk inside" binding pockets and manipulate ligands with hand controllers.

In T2DM docking studies, visualisation has been essential for interpreting binding modes. Researchers routinely generate figures showing ligands within binding sites, with key interactions highlighted. The ability to rotate, zoom, and inspect complexes from multiple angles facilitates identification of optimisation opportunities.

### 6.2 Binding Pocket Characterisation and Druggability Assessment

Binding pocket analysis quantifies geometric and physicochemical properties that determine druggability—the likelihood that a pocket can bind drug-like molecules with high affinity. Visual computing tools automate pocket detection, characterisation, and comparison.

**Pocket Detection Algorithms** identify cavities on protein surfaces using geometric (e.g., alpha shapes, Voronoi diagrams) or energy-based methods. Tools include fpocket, SiteMap, DoGSiteScorer, POVME, and CASTp. These algorithms calculate pocket volume, depth, surface area, and shape descriptors.

**Druggability Scoring** assesses pocket suitability for small molecule binding based on size, hydrophobicity, hydrogen bonding capacity, and shape complexity. SiteMap computes SiteScore and Dscore, predicting binding affinity potential. Pockets with high hydrophobic character, appropriate size (300-1000 ų), and well-defined shape are considered druggable.

**Hotspot Mapping** identifies regions contributing most to binding affinity through computational solvent mapping (FTMap) or fragment screening. Hotspots guide fragment-based design and optimization strategies.

**Pocket Comparison** aligns binding sites from different proteins or conformations, revealing conserved features and selectivity determinants. PocketMatch, SiteAlign, and ProBiS enable systematic pocket comparison.

In T2DM research, pocket characterization has informed target selection and inhibitor design. α-Glucosidase possesses a deep, well-defined active site pocket suitable for small molecule inhibition, as exploited in numerous docking studies (Ndarawit et al., 2024), (Abchır et al., 2024), (Naanaai et al., 2025), (Tong et al., 2024). DPP-4's large S1 pocket accommodates diverse hydrophobic substituents, enabling structure-based optimization (Chen et al., 2023), (Akinwumi et al., 2025). PTP1B's deep catalytic pocket presents challenges for cell-permeable inhibitor design, motivating exploration of allosteric sites (Verma & Thareja, 2016), (Ogunyemi et al., 2025).

### 6.3 Interaction Fingerprints and Contact Maps

Interaction fingerprints (IFPs) encode protein-ligand interactions as binary or weighted vectors, enabling quantitative comparison of binding

modes and systematic analysis of interaction patterns across compound series.

**Interaction Types** captured in fingerprints include hydrogen bonds (donor/acceptor), hydrophobic contacts, π-π stacking, π-cation interactions, halogen bonds, metal coordination, and salt bridges. Each interaction type is defined by geometric criteria (distance and angle thresholds).

**Fingerprint Generation** assigns bits or weights to interactions between ligand atoms/groups and protein residues. PLIF (Protein-Ligand Interaction Fingerprints), implemented in MOE and other platforms, generates per-residue interaction profiles. SPLIF (Structural Protein-Ligand Interaction Fingerprints) incorporates 3D structural information.

**Similarity Calculations** compare fingerprints using Tanimoto coefficients, Euclidean distances, or other metrics, enabling clustering of binding modes and identification of consensus interactions. Compounds with similar fingerprints likely share binding modes, while dissimilar fingerprints suggest alternative binding mechanisms.

**Visualization** of interaction fingerprints as heatmaps or network diagrams reveals patterns across compound series. Residues consistently involved in interactions represent key pharmacophoric points, while variable interactions suggest optimization opportunities.

**Contact Maps** display pairwise distances between ligand and protein atoms as 2D matrices, providing comprehensive views of binding interfaces. Time-resolved contact maps from molecular dynamics trajectories reveal dynamic interaction patterns.

In T2DM docking studies, interaction analysis has identified critical residues for inhibitor binding. Ndarawit et al. reported ionic, H-bonding, and hydrophobic interactions between lead compounds and critical amino acid residues of α-amylase and α-glucosidase (Ndarawit et al., 2024). Muppalaneni et al. identified eight hydrogen bond interactions between allium38 and aldose reductase residues Thr113, His110, Val47, and Gln49 (Muppalaneni & Rao, 2012). Systematic interaction analysis guides SAR interpretation and optimization strategies.

### 6.4 Trajectory Visualization in Molecular Dynamics

Molecular dynamics simulations generate trajectories comprising thousands of snapshots, requiring specialized visualization tools to extract meaningful insights. Trajectory analysis reveals binding stability, conformational changes, and dynamic interaction patterns not apparent from static docking poses.

**Trajectory Playback** animates molecular motion, enabling visual assessment of complex stability, ligand mobility, and protein conformational changes. VMD, PyMOL, and Maestro support trajectory loading and playback with customizable rendering.

**RMSD/RMSF Plots** quantify structural stability and flexibility. RMSD (root-mean-square deviation) measures overall structural drift from initial coordinates, while RMSF (root-mean-square fluctuation) quantifies per-residue flexibility. Stable complexes exhibit low, plateaued RMSD values. Ndarawit et al. confirmed stability of lead compounds through RMSD and RMSF analyses from 100 ns simulations (Ndarawit et al., 2024).

**Hydrogen Bond Analysis** tracks hydrogen bond formation, breaking, and occupancy throughout trajectories. Persistent hydrogen bonds (high occupancy) represent stable interactions critical for binding, while transient bonds suggest dynamic recognition.

**Distance Monitoring** tracks specific atom-atom distances (e.g., ligand-residue contacts) over time, revealing stable vs. fluctuating interactions.

**Principal Component Analysis (PCA)** identifies dominant motions in trajectories, projecting high-dimensional conformational space onto principal components. PCA reveals collective motions and conformational transitions.

**Free Energy Landscapes** constructed from trajectory data (e.g., via metadynamics or umbrella sampling) map binding pathways and energy barriers, providing thermodynamic insights.

Balogun et al. employed AMBER 18 for 100 ns molecular dynamics simulations, using PTRAJ and CPPTRAJ for post-dynamics analysis (Balogun et al., 2023). MM/GBSA calculations assessed binding free energies, revealing favorable thermodynamics for lead compounds (Balogun et al., 2023). Such comprehensive trajectory analysis validates docking predictions and identifies compounds with stable binding suitable for experimental validation.

## 7. Representative Docking Studies Organized by Target Class

### 7.1 α-Glucosidase Inhibitors

α-Glucosidase inhibitors represent the most extensively studied target class in T2DM molecular docking research, reflecting the enzyme's validated therapeutic role and availability of crystal structures.

**Natural Product Screening:** Ndarawit et al. screened the NPASS database (30,926 natural products) using molecular docking and identified NPC204580 (Chrotacumine C) and NPC137813 as dual α-amylase/α-glucosidase inhibitors (Ndarawit et al., 2024). NPC204580 exhibited binding energies of -14.46 kcal/mol (α-amylase) and -8.42 kcal/mol (α-glucosidase), while NPC137813 showed -12.58 kcal/mol (α-amylase) and -8.76 kcal/mol (α-glucosidase) (Ndarawit et al., 2024). Both compounds demonstrated ionic, H-bonding, and hydrophobic interactions with critical active site residues, with 100 ns MD simulations confirming complex stability through RMSD, RMSF, and GBSA analyses (Ndarawit et al., 2024).

**Triazole Derivatives:** Abchir et al. employed an integrative approach combining QSAR, molecular docking, ADMET analysis, and molecular dynamics to design novel triazole-based α-glucosidase inhibitors (Abchır et al., 2024). Their MLR-based QSAR model ($Q^2 = 0.652$, $R^2 = 0.954$) identified structural determinants of activity, leading to design of three compounds with high biological activity, strong binding affinity, and favorable oral bioavailability (Abchır et al., 2024). MM-GBSA calculations revealed favorable binding free energies (Abchır et al., 2024).

**Indenoquinoxaline Hybrids:** Naanaai et al. designed Indenoquinoxaline-phenylacrylohydrazide hybrids using 3D-QSAR (CoMSIA: $Q^2 = 0.652$, $R^2 = 0.954$), molecular docking, ADMET analysis, molecular dynamics, and ligand transport simulations (Naanaai et al., 2025). The most active molecule showed promising drug candidate potential for α-glucosidase inhibition (Naanaai et al., 2025).

**Metformin Derivatives:** Sulong et al. performed computational analysis and molecular dynamics simulations of metformin derivatives as α-

glucosidase inhibitors, exploring structural modifications to enhance potency (Sulong et al., 2025).

**Flavonoids:** Proença et al. investigated flavonoid α-glucosidase inhibition through combined in vitro and in silico approaches, establishing structure-activity relationships correlating hydroxylation patterns and glycosylation with inhibitory potency (Proença et al., 2017). Shah et al. explored plant-derived terpenes as α-glucosidase inhibitors using molecular docking (Shah et al., 2021).

**Phthalimide-Benzenesulfonamide Hybrids:** Askarzadeh et al. designed, synthesized, and evaluated phthalimide-benzenesulfonamide hybrids, integrating in vitro α-glucosidase inhibition assays with docking and molecular dynamics (Askarzadeh et al., 2022). The study demonstrated successful translation of computational predictions to experimental validation (Askarzadeh et al., 2022).

**Diphenylquinoxaline Derivatives:** Pedrood et al. designed and synthesized diphenylquinoxaline-6-carbohydrazide hybrids as α-glucosidase inhibitors, employing molecular docking to rationalize binding modes (Pedrood et al., 2022).

**Chalcone Hybrids:** Salim et al. conducted virtual screening of chalcone hybrids as α-glucosidase inhibitors using molecular docking and pharmacokinetic prediction (Salim et al., 2024).

**FDA Drug Repurposing:** Rashid et al. performed drug repurposing of FDA-approved compounds against α-glucosidase using molecular docking and molecular dynamics simulations, identifying existing drugs with potential antidiabetic activity (Rashid et al., 2023).

**Deep Learning Integration:** Sharma et al. integrated deep learning with molecular docking, molecular dynamics, and MMPBSA analysis to identify α-glucosidase inhibitors from phytochemicals (Sharma et al., 2024). This study exemplifies the emerging integration of AI with traditional docking workflows (Sharma et al., 2024).

### 7.2 DPP-4 Inhibitors

DPP-4 inhibitors represent a clinically validated target class, with several approved drugs (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin) providing benchmarks for computational studies.

**Structure-Based Design:** Chen et al. performed structure-based molecular docking and molecular dynamics simulations to identify DPP-4 inhibitors for T2DM (Chen et al., 2023). The study analyzed binding modes and stability of protein-ligand complexes, emphasizing interactions with the catalytic triad and S1 pocket (Chen et al., 2023).

**Natural Product Discovery:** Akinwumi et al. conducted in silico discovery of DPP-4 inhibitors from African medicinal plants using molecular docking, ADMET analysis, molecular dynamics simulations, and MM-GBSA calculations (Akinwumi et al., 2025). The study identified natural product candidates with favorable binding energies and pharmacokinetic profiles (Akinwumi et al., 2025).

**Trelagliptin Analogues:** Computational design of trelagliptin analogues has been explored through QSAR and molecular docking approaches, aiming to optimize binding affinity and selectivity [10].

**Multi-Target Approaches:** Balogun et al. identified compounds from Crescentia cujete with activity against DPP-4, α-glucosidase, and PTP1B using cheminformatics approaches (Balogun et al.,

2023). Luteolin showed binding affinity of -41.957 kcal/mol for DPP-4, with 100 ns MD simulations confirming structural stability (Balogun et al., 2023).

### 7.3 PTP1B Inhibitors

PTP1B inhibitors face challenges related to achieving cell permeability while maintaining potency, motivating computational approaches to identify compounds with balanced properties.

**Thiazolidinedione Derivatives:** Verma et al. conducted molecular docking-assisted 3D-QSAR studies of benzylidene-2,4-thiazolidinedione derivatives as PTP1B inhibitors (Verma & Thareja, 2016). The study established quantitative relationships between structural features and inhibitory potency, identifying key pharmacophoric elements including the thiazolidinedione core and benzylidene substituents (Verma & Thareja, 2016).

**Machine Learning Integration:** Ogunyemi et al. integrated machine learning-based QSAR with molecular modeling to identify PTP1B modulators from Ocimum gratissimum (Ogunyemi et al., 2025). Multiple machine learning algorithms predicted inhibitory activity, followed by molecular docking and dynamics simulations to validate binding modes (Ogunyemi et al., 2025).

**Natural Products:** Balogun et al. identified chlorogenic acid as a potent PTP1B inhibitor with binding affinity of -48.740 kcal/mol, superior to reference compounds (Balogun et al., 2023). The study employed AutoDock Vina for docking, followed by 100 ns MD simulations using AMBER 18 with FF18SB force field (Balogun et al., 2023). Post-dynamics MM/GBSA analysis revealed stable binding with favorable free energies (Balogun et al., 2023).

### 7.4 Multi-Target Inhibitors

Multi-target inhibitors address multiple pathogenic mechanisms simultaneously, potentially offering superior therapeutic outcomes compared to single-target agents.

**Dual α-Amylase/ α-Glucosidase Inhibitors:** Ndarawit et al. identified NPC204580 and NPC137813 as dual inhibitors targeting both α-amylase and α-glucosidase (Ndarawit et al., 2024). This approach addresses multiple steps in carbohydrate digestion, potentially enhancing glycemic control (Ndarawit et al., 2024).

**Multi-Enzyme Modulators:** Patil et al. performed computational assessment of substituted 2-mercaptobenzimidazole Schiff base derivatives targeting α-amylase, α-glucosidase, and PPAR-γ receptor (Patil et al., 2025). The study employed molecular docking to evaluate binding modes across multiple targets (Patil et al., 2025).

**Polypharmacological Candidates:** Balogun et al. identified luteolin and chlorogenic acid as multi-target candidates with activity against DPP-4, aldose reductase, and PTP1B (Balogun et al., 2023). Luteolin showed binding affinities of -41.957 kcal/mol (DPP-4) and -9.9 kcal/mol (aldose reductase), while chlorogenic acid exhibited -48.740 kcal/mol (PTP1B) (Balogun et al., 2023). The study proposed these compounds as candidates against T2DM and diabetic retinopathy (Balogun et al., 2023).

**Benzoquinoline Multi-Target Potential:** Pujala et al. explored the multi-targeted therapeutic potential of benzoquinoline in diabetes through molecular docking with key enzymes (Pujala & Estari, 2023).

### 7.5 Natural Product-Based Inhibitors

Natural products represent a rich source of chemical diversity for T2DM drug discovery, with traditional medicines providing ethnopharmacological leads.

**Plant-Derived Terpenes:** Shah et al. performed computational analysis of plant-derived terpenes as α-glucosidase inhibitors using molecular docking (Shah et al., 2021).

**Catharanthus roseus Ligands:** Tolambiya identified cost-effective drug candidates through in silico ligand-receptor docking of Catharanthus roseus plant compounds for T2DM (Tolambiya, 2017).

**Cyclitols:** Lalitha et al. conducted in silico ligand-receptor docking of cyclitols for type II diabetes using HEX software (Lalitha, 2011).

**Ashitaba Isolates:** Virtual screening using ligand-based pharmacophore models from Ashitaba (Angelica keiskei K.) isolates identified new α-glucosidase inhibitor candidates through molecular docking (Anne et al., 2024).

**EGCG:** Wijianto et al. performed molecular docking studies of epigallocatechin gallate (EGCG) as therapy for T2DM (Wijianto et al., 2024).

**Curculigoside A Derivatives:** Asnawi et al. employed integrative computational approaches including virtual screening, molecular docking, and molecular dynamics to design α-glucosidase inhibitors based on curculigoside A derivatives (Asnawi et al., 2024).

**African Medicinal Plants:** Akinwumi et al. discovered DPP-4 inhibitors from African medicinal plants through molecular docking, ADMET analysis, dynamics simulation, and MM-GBSA analyses (Akinwumi et al., 2025).

**Ocimum gratissimum:** Ogunyemi et al. identified PTP1B modulators from Ocimum gratissimum using machine learning-based QSAR and molecular modeling (Ogunyemi et al., 2025).

**Crescentia cujete:** Balogun et al. employed cheminformatics to identify modulators of carbohydrate-metabolizing enzymes from Crescentia cujete (Balogun et al., 2023).

## 8. Integration of Machine Learning and Artificial Intelligence in Docking Workflows

### 8.1 QSAR Modeling and Predictive Analytics

Quantitative structure-activity relationship (QSAR) modeling employs statistical and machine learning techniques to correlate molecular descriptors with biological activity, enabling prediction of compound potency prior to synthesis or experimental testing.

**Classical QSAR Approaches:** Multiple linear regression (MLR), partial least squares (PLS), and principal component regression (PCR) establish linear relationships between descriptors and activity. Abchir et al. employed MLR to generate a QSAR model ($Q^2 = 0.652$, $R^2 = 0.954$) for triazole derivatives as α-glucosidase inhibitors (Abchır et al., 2024).

**3D-QSAR Methods:** CoMFA and CoMSIA correlate 3D molecular fields (steric, electrostatic, hydrophobic, hydrogen bonding) with activity. Naanaai et al. generated a CoMSIA model ($Q^2 = 0.652$, $R^2 = 0.954$) for Indenoquinoxaline-phenylacrylohydrazide hybrids (Naanaai et al., 2025). These models provide visual contour maps indicating regions where structural modifications enhance or diminish activity.

**Machine Learning Algorithms:** Random forests, support vector machines (SVM), gradient boosting, and neural networks capture non-linear

structure-activity relationships. Ogunyemi et al. employed multiple machine learning algorithms to predict PTP1B inhibitory activity from Ocimum gratissimum compounds (Ogunyemi et al., 2025). Model performance was evaluated through cross-validation and external test sets (Ogunyemi et al., 2025).

**Descriptor Selection:** Molecular descriptors include constitutional (molecular weight, atom counts), topological (connectivity indices), geometric (3D shape descriptors), and electronic (partial charges, HOMO-LUMO energies) properties. Feature selection algorithms (e.g., genetic algorithms, LASSO) identify relevant descriptors while avoiding overfitting.

**Model Validation:** Internal validation through cross-validation (leave-one-out, k-fold) and external validation using independent test sets assess model predictive power. Metrics include $Q^2$ (cross-validated $R^2$), $R^2$ (coefficient of determination), RMSE (root-mean-square error), and MAE (mean absolute error).

**Integration with Docking:** QSAR models complement docking by providing rapid activity predictions for large libraries, enabling prioritization of compounds for detailed docking studies. Conversely, docking-derived descriptors (binding energies, interaction counts) can serve as QSAR features.

### 8.2 Deep Learning for Binding Affinity Prediction

Deep learning models, particularly deep neural networks and graph neural networks, have demonstrated superior performance in binding affinity prediction compared to classical scoring functions.

**Convolutional Neural Networks (CNNs):** 3D-CNNs process voxelized representations of protein-ligand complexes, learning spatial patterns associated with binding. Models such as DeepBind, DeepDTA, and Pafnucy predict binding affinities from 3D structures.

**Graph Neural Networks (GNNs):** GNNs represent molecules as graphs (atoms as nodes, bonds as edges) and learn embeddings capturing chemical structure. Models including GCN (Graph Convolutional Networks), GAT (Graph Attention Networks), and MPNN (Message Passing Neural Networks) predict molecular properties and binding affinities.

**Transformer Architectures:** Attention-based models process molecular sequences (SMILES, amino acid sequences) to predict interactions. Models such as MolBERT and ChemBERTa leverage pre-training on large chemical databases.

**Protein-Ligand Interaction Prediction:** Models trained on large datasets (PDBbind, BindingDB) predict binding affinities with higher accuracy than classical scoring functions. DeepDTA and GraphDTA predict drug-target affinities from molecular and protein sequences.

**Transfer Learning:** Pre-trained models on large datasets can be fine-tuned for specific targets or compound classes, reducing data requirements and improving performance.

**Integration with Docking:** Deep learning models can serve as scoring functions within docking workflows, rescoring docked poses to improve ranking accuracy. Sharma et al. integrated deep learning with molecular docking to identify α-glucosidase inhibitors from phytochemicals (Sharma et al., 2024).

### 8.3 AI-Driven Virtual Screening

Artificial intelligence accelerates virtual screening by rapidly predicting compound activity, prioritizing candidates for detailed docking, and identifying novel scaffolds.

**Active Learning:** Iterative workflows where machine learning models predict compound activity, top candidates are experimentally tested, and results are fed back to retrain models. This approach efficiently explores chemical space with minimal experimental effort.

**Generative Models:** Variational autoencoders (VAEs), generative adversarial networks (GANs), and reinforcement learning models generate novel molecular structures optimized for target binding. Models such as REINVENT, MolGAN, and JT-VAE design compounds de novo.

**Multi-Objective Optimization:** AI models optimize multiple objectives simultaneously (potency, selectivity, ADMET properties, synthetic accessibility), identifying compounds with balanced profiles.

**Explainable AI:** Interpretable models and attention mechanisms reveal which molecular features drive predictions, guiding medicinal chemistry optimization.

**Benchmark Studies:** AI-driven virtual screening has identified active compounds in retrospective studies, demonstrating potential to accelerate drug discovery. Prospective applications in T2DM research are emerging, with integration of AI into docking workflows representing a future direction.

## 9. Limitations and Critical Assessment

### 9.1 Scoring Function Accuracy and Ranking Power

Scoring functions remain the Achilles' heel of molecular docking, with limited accuracy in absolute binding affinity prediction and imperfect ranking of compounds. Typical scoring function errors range from 2-3 kcal/mol, corresponding to 50-100 fold uncertainty in binding affinity. This limitation arises from simplified treatment of solvation, entropy, and polarization effects.

**Ranking vs. Scoring:** Scoring functions perform better at ranking compounds (identifying relative potency) than predicting absolute binding affinities. However, even ranking accuracy is imperfect, with enrichment factors in virtual screening often modest.

**Target Dependence:** Scoring function performance varies across targets, with some proteins yielding better predictions than others. Calibration on target-specific datasets can improve accuracy.

**Consensus Scoring:** Combining multiple scoring functions improves reliability, as demonstrated by Muppalaneni et al., who employed consensus scoring across GOLD, AutoDock Vina, eHiTS, PatchDock, and MEDock (Muppalaneni & Rao, 2012). However, consensus scoring increases computational cost and does not guarantee accuracy.

**Machine Learning Scoring:** Deep learning models trained on large datasets show promise for improved scoring, though generalization to novel targets and scaffolds remains challenging.

### 9.2 Protein Flexibility and Induced Fit

Most docking algorithms treat proteins as rigid, neglecting conformational changes upon ligand binding (induced fit). This approximation limits accuracy, particularly for flexible binding sites or allosteric pockets.

**Ensemble Docking:** Using multiple protein conformations (from crystal structures, NMR

ensembles, or MD simulations) partially addresses flexibility. However, selecting representative conformations and combining results remain challenges.

**Flexible Docking:** Some algorithms allow limited protein flexibility (side chain rotations, backbone adjustments), but computational cost increases significantly.

**Molecular Dynamics Refinement:** Post-docking MD simulations, as employed by Ndarawit et al. (Ndarawit et al., 2024), Balogun et al. (Balogun et al., 2023), and others, allow full protein-ligand relaxation and assess binding stability. This approach is computationally intensive but provides more realistic models.

**Allosteric Sites:** Docking to allosteric sites, which often undergo large conformational changes, is particularly challenging and may require advanced techniques such as metadynamics or Markov state models.

### 9.3 Solvation and Entropy Effects

Accurate treatment of solvation and entropy is critical for binding affinity prediction but remains computationally challenging.

**Solvation Models:** Implicit solvent models (Generalized Born, Poisson-Boltzmann) approximate solvent effects efficiently but with limited accuracy. Explicit solvent simulations (MD with water molecules) are more accurate but computationally expensive.

**Desolvation Penalties:** Ligand and protein desolvation upon binding contributes unfavorably to binding free energy. Scoring functions approximate desolvation through surface area terms or implicit solvent models, but accuracy is limited.

**Entropy Contributions:** Conformational entropy loss upon binding (ligand and protein) opposes binding. Estimating entropy changes requires extensive sampling (e.g., normal mode analysis, quasi-harmonic analysis), which is computationally demanding.

**Water-Mediated Interactions:** Conserved water molecules in binding sites can mediate protein-ligand interactions. Deciding whether to retain or remove crystallographic waters affects docking accuracy. Advanced methods (e.g., WaterMap, GRID) predict water positions and thermodynamic contributions.

### 9.4 Validation and Experimental Correlation

Computational predictions require experimental validation to confirm activity and binding modes. Discrepancies between predictions and experiments arise from multiple sources.

**Crystal Structure Validation:** Co-crystallization of predicted complexes provides definitive validation of binding modes. However, crystallization is time-consuming and not always successful.

**Biochemical Assays:** In vitro enzyme inhibition or binding assays ($IC_{50}$, K_i, K_d) validate predicted potency. Correlation between predicted binding energies and experimental affinities is often modest.

**Cell-Based Assays:** Cellular activity depends on permeability, efflux, metabolism, and target engagement, factors not captured by docking. Compounds with strong predicted binding may show weak cellular activity.

**Retrospective vs. Prospective Studies:** Most published docking studies are retrospective (rationalizing known actives), which may overestimate predictive power. Prospective studies

(predicting then testing novel compounds) provide more rigorous validation.

**Publication Bias:** Successful docking studies are more likely to be published than unsuccessful ones, potentially inflating perceived accuracy.

## 10. Future Directions and Emerging Paradigms

### 10.1 Multi-Target and Polypharmacology Approaches

The multifactorial nature of T2DM motivates multi-target drug design, where single compounds modulate multiple pathogenic pathways. Computational approaches can identify polypharmacological agents through multi-target docking and network pharmacology.

**Multi-Target Docking:** Docking compounds against multiple T2DM targets (α-glucosidase, DPP-4, PTP1B, PPAR-γ, etc.) identifies compounds with balanced activity profiles. Balogun et al. demonstrated this approach by identifying luteolin and chlorogenic acid with activity against multiple targets (Balogun et al., 2023).

**Network Pharmacology:** Systems biology approaches integrate protein-protein interaction networks, pathway analysis, and multi-target docking to identify compounds modulating disease networks rather than single targets.

**Selectivity Optimization:** Designing compounds with desired selectivity profiles (e.g., dual inhibition of α-glucosidase and α-amylase while avoiding off-targets) requires multi-objective optimization.

### 10.2 Fragment-Based Drug Design

Fragment-based drug design (FBDD) identifies small molecular fragments (MW < 300 Da) binding weakly to targets, then links or grows fragments into potent leads. FBDD explores chemical space efficiently and often yields ligand-efficient compounds.

**Fragment Screening:** Computational fragment screening uses docking to identify fragments binding to target sites. Experimental validation employs biophysical techniques (SPR, NMR, X-ray crystallography).

**Fragment Linking:** Linking fragments binding to adjacent sites creates larger molecules with enhanced affinity. Computational tools predict optimal linkers and assess synthetic feasibility.

**Fragment Growing:** Extending fragments into adjacent pockets increases potency and selectivity. Docking guides growth directions and substituent selection.

**Application to T2DM:** FBDD has been applied to kinases and proteases but remains underexplored for T2DM targets. Future studies could leverage FBDD for α-glucosidase, DPP-4, and PTP1B inhibitor design.

### 10.3 Covalent Docking and Allosteric Modulation

**Covalent Inhibitors:** Covalent drugs form irreversible or reversible covalent bonds with target residues, offering prolonged duration of action and high potency. Covalent docking algorithms (e.g., CovDock, GOLD covalent docking) model covalent bond formation and predict binding modes. Covalent DPP-4 inhibitors (saxagliptin) and covalent SGLT2 inhibitors represent potential applications.

**Allosteric Modulators:** Allosteric sites, distinct from active sites, offer opportunities for selective modulation. Allosteric docking requires identifying cryptic pockets and modeling

conformational changes. Metadynamics and Markov state models facilitate allosteric site discovery. PTP1B allosteric inhibitors have been explored computationally, offering potential for cell-permeable compounds.

### 10.4 Quantum Mechanics/Molecular Mechanics (QM/MM) Integration

QM/MM methods treat critical regions (e.g., active sites, ligands) with quantum mechanics while modeling the remainder with molecular mechanics. This approach accurately captures electronic effects (polarization, charge transfer, bond formation or breaking) critical for catalysis and covalent binding.

**Applications:** QM/MM is valuable for modeling enzyme mechanisms, transition states, and covalent inhibitors. For T2DM targets, QM/MM could elucidate α-glucosidase catalytic mechanisms, guiding transition state analogue design.

**Computational Cost:** QM/MM is computationally expensive, limiting applications to small systems or short simulations. Advances in algorithms and hardware are expanding feasibility.

### 10.5 Generative AI for De Novo Design

Generative AI models design novel molecular structures optimized for target binding, ADMET properties, and synthetic accessibility.

**Generative Models:** VAEs, GANs, and reinforcement learning models generate molecules *de novo*. REINVENT, MolGAN, and JT-VAE have designed compounds with desired properties.

**Conditional Generation:** Models conditioned on target structures or pharmacophores generate compounds tailored to specific binding sites.

**Multi-Objective Optimization:** Generative models optimize multiple objectives (potency, selectivity, ADMET, synthetic accessibility) simultaneously, identifying compounds with balanced profiles.

**Integration with Docking:** Generative models propose candidates, which are evaluated by docking and ADMET prediction. Iterative cycles refine designs.

**Application to T2DM:** Generative AI could design novel α-glucosidase, DPP-4, or PTP1B inhibitors with optimized properties. Integration with experimental validation would accelerate discovery.

## CONCLUSION

Molecular docking has established itself as an indispensable tool in the computational drug discovery arsenal for type 2 diabetes mellitus, enabling rapid virtual screening, rational ligand design, and mechanistic understanding of protein-ligand interactions. This comprehensive review has examined the application of docking methodologies to key T2DM targets including α-glucosidase, α-amylase, DPP-4, PTP1B, PPAR-γ, GLUT, SGLT2, and aldose reductase, revealing a rich landscape of chemical scaffolds, binding modes, and structure-activity relationships.

From a medicinal chemist's perspective, molecular docking transcends computational prediction, serving as an integrated platform for hypothesis generation, pharmacophore identification, SAR analysis, and lead optimization. The synergy between docking predictions and experimental validation, exemplified by studies integrating *in vitro* assays with computational workflows, accelerates the drug discovery timeline and enhances the probability of identifying clinically viable candidates. The incorporation of ADMET

profiling and drug-likeness assessment ensures that computational efforts prioritize compounds with favourable pharmacokinetic and safety profiles.

Visual computing technologies have transformed molecular docking from abstract numerical predictions into intuitive 3D representations, enabling interactive exploration of binding modes, systematic pocket characterization, and comprehensive interaction mapping. The ability to visualize and manipulate protein-ligand complexes in real-time facilitates chemical intuition and guides optimization strategies. Trajectory visualization from molecular dynamics simulations provides dynamic insights into binding stability and conformational changes, validating static docking predictions.

Representative studies across target classes demonstrate the diversity of computational approaches and chemical scaffolds explored for T2DM therapy. Natural product screening has identified dual α-amylase/α-glucosidase inhibitors with favorable binding energies and stability profiles. Triazole, indenoquinoxaline, phthalimide-benzenesulfonamide, and diphenylquinoxaline derivatives have emerged as privileged scaffolds for α-glucosidase inhibition. DPP-4 inhibitor discovery has leveraged structure-based design and natural product exploration. PTP1B inhibitor development has integrated machine learning with molecular modeling to identify compounds with balanced potency and cell permeability. Multi-target inhibitors addressing multiple pathogenic mechanisms represent an emerging paradigm with potential for superior therapeutic outcomes.

The integration of machine learning and artificial intelligence with traditional docking workflows marks a transformative shift in computational drug discovery. QSAR modeling provides rapid activity predictions for large libraries, while deep learning models demonstrate superior binding affinity prediction compared to classical scoring functions. AI-driven virtual screening, active learning, and generative models accelerate compound identification and enable de novo design of molecules optimized for multiple objectives. The synergy between physics-based docking and data-driven AI approaches promises to overcome limitations of individual methods.

Despite significant advances, molecular docking faces persistent challenges including scoring function accuracy, protein flexibility representation, solvation modeling, and entropy estimation. Scoring function errors of 2–3 kcal/mol limit absolute binding affinity prediction, although ranking performance is more reliable. Rigid protein approximations neglect induced fit effects, motivating ensemble docking and molecular dynamics refinement. Solvation and entropy contributions remain computationally challenging, requiring advanced techniques such as explicit solvent simulations and free energy calculations. Experimental validation through biochemical assays, cell-based studies, and structural biology remains essential to confirm computational predictions.

Future directions in T2DM computational drug discovery include multi-target and polypharmacology approaches addressing the multifactorial nature of the disease, fragment-based drug design exploring chemical space efficiently, covalent docking and allosteric modulation offering novel mechanisms of action, QM/MM integration capturing electronic effects critical for catalysis, and generative AI enabling de novo design of optimized compounds. The convergence of structural biology, computational chemistry, machine learning, and visual

computing creates unprecedented opportunities for next-generation antidiabetic therapeutics.

As the global burden of type 2 diabetes mellitus continues to escalate, the imperative for innovative therapeutic strategies intensifies. Molecular docking, enhanced by visual computing and artificial intelligence, stands poised to accelerate the discovery of safer, more effective antidiabetic agents. By bridging computational predictions with experimental validation and clinical translation, the field moves toward a future where computational drug design plays a central role in addressing one of humanity's most pressing health challenges.

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HOW TO CITE: Dr. Bolie Therattil, Molecular Docking Studies in Type 2 Diabetes Mellitus Drug Discovery: A Chemist's Perspective on Computational Design and Visual Analytics, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 6159-6186. https://doi.org/10.5281/zenodo.21726913